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[Intervention Protocol]

Intermittent prophylactic antibiotics for bronchiectasis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the safety and efficacy of intermittent prophylactic antibiotics in the treatment of adults and children with bronchiectasis.

BACKGROUND

Description of the condition

Bronchiectasis is a common but, until recently, underdiagnosed chronic disorder characterised by permanent dilation of the large airways, bronchi and bronchioles (branches of the bronchi) (Pasteur 2010). This arises from a vicious cycle of respiratory infections that cause inflammation and damage to the bronchial walls, leading to disordered mucociliary clearance (mucus-clearing mechanism of the bronchi), that in turn renders patients more susceptible to recurrent infections (Chalmers 2013; Cole 1986). An understanding of this cycle of recurrent infection and tissue destruction is important in the management of bronchiectasis, where the central aim is to limit the progression of lung injury by arresting inflammation and bacterial colonisation (Cole 1997; Pasteur 2010). The most commonly isolated microorganisms include non-typeable *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Moraxella catarrhalis* (Foweraker 2011). Organisms such as *P. aeruginosa*, *H. influenzae* and *M. catarrhalis* are often resistant to antimicrobial therapy arising from intrinsic resistance mechanisms and frequent exposure to antimicrobial agents (Menendez 2017).

Bronchiectasis presents with chronic, persistent cough, productive phlegm that is frequently difficult to expectorate, and recurrent respiratory infections, posing a significant health burden (Chalmers 2014). The cause of around half of presenting cases are unknown and classified as idiopathic (cause is unknown), but the most common aetiology is post-infectious bronchiectasis, a diverse group that includes people with childhood respiratory infections such as pertussis, bacterial pneumonia, or tuberculosis (Pasteur 2010). Diagnosis is based on the presence of one or more abnormally dilated bronchi using high resolution computed tomography (HRCT) (Chang 2010; Pasteur 2010). The central aims of

therapeutic management are to reduce symptoms such as cough, breathlessness and expectoration, to reduce the frequency and duration of exacerbations, and to improve quality of life (Chalmers 2015; Pasteur 2010).

Recent epidemiological studies have suggested that the prevalence of bronchiectasis is increasing, particularly in women and those over 60 years old (Roberts 2010; Seitz 2010; Weycker 2005), with higher rates in low- and middle- income countries (Habesoglu 2011). In Germany, prevalence has been estimated at 67 cases per 100,000 general population (Ringshausen 2015). Recent UK figures estimate 263,000 adults living with bronchiectasis in 2013, with prevalence rates per 100,000 rising by approximately 60% over a nine-year period, from 350.5 to 566.1 in women and from 301.2 to 485.5 in men (Quint 2016). Similarly, approximately 15,000 new cases were identified in 2013, with incidence rates per 100,000 person-years rising by around 63% over the same nine year period, from 21.2 to 35.2 in women and from 18.2 to 26.9 in men. European mortality rates, based on 2005 to 2009 data, are estimated at 0.3 per 100,000 general population in EU countries and at 0.2 per 100,000 general population in nine non-EU countries (Gibson 2013). Age-adjusted mortality in the UK is estimated to be 2.3 times higher in women and 2.1 times higher in men compared to the general population (Quint 2016).

The impact of bronchiectasis on children is significant, with worse quality of life in younger children and those with more frequent exacerbations (Kapur 2012). Global prevalence is highly variable with higher rates in some indigenous groups, such as 15 per 1000 in Australian Aboriginal and Torres Strait Islander children and 16 per 1000 among southwest Alaskan children (Chang 2002). The incidence rate in one New Zealand study was 3.7 per 100,000 per year in under 15 year olds, with an overall prevalence of 1 per 3000 children, but a much higher rate of 1 per 625 in Pacific children (Twiss 2005). These rates were almost seven times higher than those in Finland (Twiss 2005).

Higher prevalence rates may be attributable to improvements in diagnosis resulting from high resolution CT (HRCT) scans and heightened awareness of bronchiectasis symptoms, rather than a true increase in the spread of the condition (Goeminne 2016).

Bronchiectasis is associated with a high rate of exacerbations, hospital admissions, and attributable mortality, which places a considerable burden on international healthcare systems (Chalmers 2015; Redondo 2016). Approximately half of patients on the European bronchiectasis registry have at least two exacerbations per year and a third of those on the registry are hospitalised at least once a year (Polverino 2017). Patients with more frequent annual exacerbations and those colonised with *P. aeruginosa* have a more rapid decline in lung function, worse health-related quality of life and a higher risk of hospitalisation and mortality (Evans 1996; Martínez-García 2007; Polverino 2017; Wilson 1997). Other risk factors for higher hospitalisation and mortality rates include; severe exacerbations, low body mass index, chronic bacterial infection, low forced expiratory volume in one second (FEV1) percent of predicted, a higher proportion of affected lobes, and more breathlessness (Chalmers 2014; Rogers 2014; Seitz 2010).

The high burden of bronchiectasis is associated with substantial costs of care. The annual mean direct medical costs for an adult with bronchiectasis was estimated at EUR 4671 in a Spanish study, with higher costs associated with more severe disease (De la Rosa 2016). In a USA-based study, the additional costs of care for bronchiectasis patients compared to matched case-controls were associated with an annual increase of USD 2319 in overall costs and USD 1607 in respiratory-related costs (Joish 2013).

Bronchiectasis is the primary manifestation of genetic diseases such as cystic fibrosis, primary ciliary dyskinesia (impaired movement) or hypogammaglobulinaemia (immune disorder characterised by reduced resistance to infection). Such cases are characterised by more severe clinical presentation and worse outcomes and are beyond the scope of this systematic review. Bronchiectasis is also associated with other diseases, such as chronic obstructive pulmonary disease (COPD). Patients with both COPD and bronchiectasis have worse outcomes, especially those who continue to smoke, and are therefore regarded as a separate population and beyond the remit of this review (Lanza 2018, Ni 2015).

Description of the intervention

Prophylactic antibiotic therapy is a cornerstone of the management of patients with bronchiectasis, its goal being to suppress bacterial infection and to break the vicious cycle of recurrent infections and exacerbations, with resultant reductions in bacterial load, inflammation, and consequent tissue destruction of the airways (Chalmers 2012). To date, randomised controlled trials (RCTs) of antibiotics in bronchiectasis have evaluated different modes (oral, intravenous (IV) and inhaled) and methods (continuous versus intermittent) of administration, using different classes of antibiotics, including but not limited to macrolides, quinolones, and polymyxins. Pooled data on the use of long-term prophylactic antibiotics administered for three or more months have demonstrated antibiotics efficacy for patients with frequent bronchiectasis exacerbations in decreasing the frequency and severity of exacerbations, increasing the time to first exacerbation and reducing symptom burden, offset by an increased adverse event profile and increased bacterial resistance (Hnin 2015; Polverino 2017). Continuous antibiotics are associated with more than three times the risk of bacterial resistance compared to no antibiotic prophylactic therapy (Hnin 2015).

In clinical practice, antibiotics are most frequently used in patients with three or more exacerbations per year, in patients with chronic *P. aeruginosa* infection and also in patients with less frequent exacerbations who continue to have significant impairment of quality of life despite standard treatment (Chalmers 2015; Polverino 2017). Intermittent therapy refers to the repeated prophylactic administration of courses of antibiotics with predefined duration and intervals. Examples include antibiotics given every month or

drug holidays with treatment during the winter months only to allow for seasonal variations. As the half-life of antibiotics, such as azithromycin, is approximately one week, the off-treatment interval should last at least 14 days. Prophylactic antibiotics may be given for regimens of at least 14 days on-treatment followed by at least 14 days off-treatment, for cycles lasting at least three months (Polverino 2017). In this review, we will compare the administration of intermittent long-term antibiotics using different duration periods, or compared with placebo, over three months or longer. This definition excludes short courses of antibiotics for acute exacerbations, which have been addressed in a separate review (Wurzel 2011).

How the intervention might work

Chronic airway infection is central to the pathogenesis (development) of bronchiectasis. The presence of airway bacteria results in neutrophilic (white blood cells) inflammation which promotes airway destruction and disease progression (Chalmers 2012; Chalmers 2017). It is therefore logical that suppression of bacterial load should reduce symptoms and prevent exacerbations. Antibiotic treatment has been proven to reduce bacterial load and to thereby reduce neutrophilic inflammation (Chalmers 2012). Gram-negative pathogens and *P. aeruginosa,* in particular, are associated with a significant increase in the risk of death over five years compared to other pathogens, even after adjustment for confounders (Araujo 2018; Finch 2015).

As clinical outcomes are better in patients without bacterial infection, continuous long-term suppression of airway bacteria is an important aim (Polverino 2017). However, the argument against continuous exposure to antibiotics is that it leads to increased bacterial resistance and consequently treatment may lose its effectiveness (Chalmers 2015). On the contrary, intermittent administration of antibiotics might remove or limit antibiotic selection pressure and, consequently, prevent the development of resistance. There is often a fitness cost for bacteria acquiring antimicrobial resistance which means that once the selection pressure is removed the resistant organism is 'out-competed' by non-resistant organisms (Melnyk 2015). Indirect evidence of this concept is provided by a large retrospective analysis of mechanically-ventilated patients with hospital-acquired (nosocomial) infections (40% chronic lung disease) where an interval of at least 20 days between serial courses of antibiotics was associated with a 24% reduction in development of resistance (Hui 2013). Additionally, some antibiotic agents appear to have problems with tolerability and an increased risk of antibiotic-related adverse events which may be minimised with intermittent therapy. Also, the treatment burden associated with nebulised therapies (inhaled as a mist), including both the time to administer the dose and to care for the machinery, are substantial and so less frequent administration may improve treatment adherence and limit total costs (Chalmers 2015; McCullough 2014).

Why it is important to do this review

The 2017 ERS (European Respiratory Society) guidelines for bronchiectasis recommended the use of long-term antibiotics for patients with three or more exacerbations per year following treatment of the underlying cause and regular airway clearance exercises (Polverino 2017). There are currently no clinical trials that compare the safety and efficacy of continuous administration with intermittent administration of antibiotics (Donovan 2018) and the optimal delivery route (oral, inhaled, IV), dosage, and duration of intermittent antibiotics remain unclear. Given the theoretical balance between bacterial suppression and prevention of resistance, it is important to synthesise the available data on the safety and efficacy of intermittently administered antibiotic treatments in bronchiectasis to determine their impact on the prevention of exacerbations.

OBJECTIVES

To evaluate the safety and efficacy of intermittent prophylactic antibiotics in the treatment of adults and children with bronchiectasis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised and cluster-randomised controlled trials (RCTs). We will also include cross-over studies but, to overcome potential carry-over effects from the first phase (e.g. antibiotic resistance), we will only use data from the first pre-cross-over phase. We will include studies reported in full text, those only published as abstracts, and unpublished data.

Types of participants

We will include adults and children (< 18 years) with a clinical diagnosis of bronchiectasis confirmed by high resolution computed tomography (HRCT), plain film chest radiograph, or bronchography and a documented history of recurrent chest infections. We will exclude studies where participants received high dose antibiotics immediately prior to enrolment or those with a diagnosis of allergic bronchopulmonary aspergillosis (ABPA), hypogammaglobulinaemia, cystic fibrosis (CF), sarcoidosis, or a primary diagnosis of COPD. We will also exclude studies where participants receive short courses of antibiotics for an acute exacerbation. We

will only include studies with mixed populations (different respiratory conditions), if there is a separate subgroup analysis for participants with bronchiectasis. Data on children and adults will be analysed separately.

Types of interventions

We will include studies comparing the following:

- Prophylactic intermittent antibiotics versus placebo.
- Prophylactic intermittent antibiotics versus usual care.

Usual care may include bronchodilators, anti-inflammatories, mucolytics, inhaled hyperosmolar agents, or chest physiotherapy.

- Prophylactic intermittent antibiotics using regimen X versus regimen Y, e.g. 14 days of antibiotics followed by 14 days of none versus 28 days of antibiotics followed by 28 days of none.

These different comparisons will be reported separately. Intermittent prophylactic administration is defined as repeated courses of antibiotics with predefined on-treatment duration of at least 14 days and off-treatment intervals of at least 14 days, for a study duration of at least three months. The method of administration may be oral or inhaled, but should be the same in all study groups in order to isolate the effect of the antibiotic rather than the delivery device. We will exclude studies that compare continuously administered prophylactic antibiotics with those administered intermittently as this has been addressed in a separate review (Donovan 2018).

Types of outcome measures

We will use exacerbation and hospitalisation rates as reported by study authors. We will collect outcome data at a range of follow-up points that best reflect available evidence from included studies (e.g. end of study, end of follow-up, change from baseline).

Primary outcomes

1. Frequency of exacerbations (defined using study authors' criteria).
2. Serious adverse events defined as follows: adverse events resulting in death or life-threatening events, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or congenital anomalies, or events considered medically important (Hansen 2015).

Secondary outcomes

1. Time to first exacerbation (defined using study authors' criteria).
2. Duration of exacerbations (defined using study authors' criteria).
3. Severity of exacerbations (defined using study authors' criteria).
4. Development of antibiotic resistance (defined using study authors' criteria).
5. Frequency of hospital admissions due to exacerbations (defined using study authors' criteria).
6. Frequency of hospital admissions (defined using study authors criteria).
7. Lung function measured as forced expiratory volume in one second (FEV_1).
8. Health-related quality of life using measures validated in a clinical setting (e.g. St George's Respiratory Questionnaire (SGRQ), Leicester Cough Questionnaire (LCQ) or Quality of Life-Bronchiectasis (QoL-B)).
9. Adverse effects and adverse reactions defined as follows. Adverse effects are unwanted outcomes of which the patient is not aware, usually detected by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation). Adverse reactions are unwanted outcomes that the patient experiences and are detected by their clinical manifestations (symptoms and/or signs) (Hansen 2015).

The above outcomes will not be not used as eligibility criteria for inclusion of studies in the review. Study selection will be based on types of studies, participants, and interventions, to avoid excluding eligible studies with unpublished review outcomes.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
2. weekly searches of MEDLINE Ovid SP 1946 to date;
3. weekly searches of Embase Ovid SP 1974 to date;
4. monthly searches of PsycINFO Ovid SP 1967 to date;
5. monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date;
6. monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will search the following trials registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search the Cochrane Airways Trials Register and additional sources from inception to present, with no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references and search relevant manufacturers' websites for study information.

We will also search for errata or retractions from included studies published in full text on PubMed and report the date of the search in the review.

Data collection and analysis

Selection of studies

Two review authors (TD and MMD) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (TD and MMD) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (SS). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection using a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (AT) will extract the following study characteristics from included studies:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

We will summarise the interventions in included studies (study, adults or children, number of participants, type of antibiotic, dose, frequency, regimen, delivery mode, comparator) using a study characteristics table.

Two review authors (AT and GP) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (SS). One review author (AT) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (GP) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SS and TD) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (MMD). We will assess the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We will judge each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes, where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).
We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.
We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).
Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.
We will use adjusted date as first choice if it is available (e.g. rate ratios from Poisson regression models, mean differences from ANOVAs or results from cluster-RCTs adjusted for the effects of clustering), followed by change scores and endpoint scores.
We will use intention-to-treat (ITT) analyses where they are reported instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of people admitted to hospital, rather than number of admissions per person). However, if exacerbations and hospitalisations are reported as rate ratios (number of events experienced by a participant) in a study, we will analyse them on this basis.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data, where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity (> 50%) we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will use a random-effects model, reported with 95% confidence intervals (CI) and perform a sensitivity analysis with a fixed-effect model. We will synthesise and report dichotomous and continuous data separately for each outcome, e.g. hospitalisation/no hospitalisation or duration of hospitalisation. Data on adults and children will be reported separately. Odds ratios will also be analysed and reported separately. For a given outcome measure, we will combine effect estimates, such as differences at endpoint and change from baseline, providing that there are no reported baseline differences between groups, When outcomes are measured using different scales, e.g. health-related quality of life, we will use standardised mean differences (SMD) in the analyses. We will use the baseline standard deviation (SD) for the SMD analyses.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: frequency of exacerbations, serious adverse events, development of antibiotic resistance, frequency of hospital admissions, and health-related quality of life. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review, where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. Colonisation with *P aeruginosa* at study enrolment versus no colonisation;
2. Method of administration (oral versus IV versus inhaled).

We will use the following outcomes in subgroup analyses:

1. Exacerbation frequency;
2. Serious adverse events.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out sensitivity analyses by comparing results before and after removing studies at high risk of bias from:

1. Random sequence generation;
2. Allocation concealment.

We will also compare the results from a fixed-effect model with results from the random-effects model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly

(*Continued*)

EMBASE (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the Cochrane Airways Trials Register

Bronchiectasis search

1. exp Bronchiectasis/
2. bronchiect$.mp.
3. bronchoect$.mp.
4. kartagener$.mp.
5. (ciliary adj3 dyskinesia).mp.
6. (bronchial$ adj3 dilat$).mp.
7. or/1-6

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

Search line	Search terms	Comments
#1	BRONCH:MISC1	MISC1 denotes the field in the record where the record has been coded for condition, in this case, bronchiectasis
#2	MeSH DESCRIPTOR Bronchiectasis Explode All	Index term for bronchiectasis, exploded to retrieve all narrower terms
#3	bronchiect*	
#4	#1 or #2 or #3	search line combines all population terms
#5	MeSH DESCRIPTOR Anti-Bacterial Agents Explode 1	Index term for antibiotics, exploded to retrieve all narrower terms
#6	antibiotic* or anti-biotic*	
#7	anti-bacteri* or antibacteri*	
#8	*cillin	
#9	*mycin OR *micin	
#10	*oxacin	
#11	*tetracycline	
#12	macrolide*	
#13	quinolone*	
#14	trimethoprim	

(*Continued*)

#15	ceph*	
#16	sulpha*	
#17	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	search line combines all intervention terms
#18	#4 and #17	search line brings together population and intervention terms

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the Background section. TD, AT, GP, and SS contributed to the Methods section.

AT will search trial registries, TD and MMD will screen the search results, AT and GP will extract data, TD and SS will complete the 'risk of bias' assessment, SS and AT will undertake data analysis, and all review authors will contribute to writing of the report.

DECLARATIONS OF INTEREST

S. Spencer: was the lead investigator on a study to develop a series of reviews on bronchiectasis, funded by Edge Hill University. She is an editor for the Cochrane Airways Group and the Cochrane Dementia and Cognitive Improvement Group.

T. Donovan: none known

J.D. Chalmers: member of the EMBARC group that set research priorities in bronchiectasis. He also receives grant support from Pfizer, AstraZeneca, and GlaxoSmithKline. In addition, he is part of an innovative medicines initiative consortium that includes Novartis and Basilea Pharmaceutica. He has participated in advisory boards for Bayer HealthCare, Chiesi, and Raptor Pharmaceuticals. He has received speaker fees from Napp, AstraZeneca, BI, and Pfizer. None of these conflicts of interest are related to the work of this review and are unrelated to the topic of the review.

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